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CLINICAL STUDY

Characteristics of blood glucose excursions in type 2 diabetes mellitus patients with three different Traditional Chinese Medicine syndromes

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Abstract

OBJECTIVE: To explore the characteristics of blood glucose excursions of type 2 diabetes mellitus patients with three different Traditional Chinese Medicine (TCM) syndromes.

METHODS: One hundred and nine patients with type 2 diabetes mellitus were recruited from the Department of Endocrinology and the Department of TCM of the Sixth People's Hospital affiliated to Shanghai Jiao Tong University. Subjects were divided into three groups according to TCM syndrome: intrinsic Damp (n = 42), *Yin* deficiency and internal Heat (n = 25), and *Qi* and *Yin* deficiency (n = 42). Subcutaneous interstitial glucose was monitored with a continuous glucose monitoring system for 3 consecutive days to investigate the glycemic profile in each group. Plasma C-peptide levels were measured, and an arginine test was taken in 10 patients randomly selected from each group. Glucose data and glycemic variability were analyzed to investigate the differences among the groups. The change in C-peptide levels and the results from arginine trial were used to evaluate β cell function.

RESULTS: Indicators reflecting blood glucose level were the highest in subjects with *Yin* deficiency and internal Heat syndrome, and parameters reflecting glycemic variability were the lowest in those with *Qi* and *Yin* deficiency syndrome. The change in C-peptide levels showed that subjects with *Qi* and *Yin* deficiency syndrome had the best β cell function among the three groups; this was confirmed by the arginine trial.

CONCLUSION: Patients with *Qi* and *Yin* deficiency syndrome had a more stable blood glucose profile, as glycemic variability was higher in those with intrinsic Damp syndrome and those with *Yin* deficiency and internal Heat syndrome.

Key words: Blood glucose excursions; Glycemic variability; Symptom complex; Diabetes mellitus, type 2

INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) is increasing every year, becoming the third biggest killer of humans following cancer and cardiovascular disease.[1,2] Moreover, T2DM is closely related to the occurrence of cancer and cardiovascular disease.[3] Therefore, more attention worldwide has been paid to T2DM in recent years. Recognizing the characteristics of the blood glucose (BG) profile is necessary for doctors and patients to control BG and delay complications of T2DM both in Western Medicine and Traditional Chinese Medicine (TCM).

The effect of the T2DM treatment regimen is usually assessed by measuring fasting BG and postprandial BG levels, which can only reflect the instant BG level; however, glycolated hemoglobin (HBA1C) reflects the average BG level of the previous 2-3 months.[4] The continuous glucose monitoring system (CGMS) is a new technology applied in clinical practice that can provide a continuous glycemic profile and best reflect the individuals' current BG status.[5] Doctors can then use this CGMS profile to design the optimal individual treatment regimen. Many previous studies have demonstrated that BG variability rather than hyperglycemia alone contributes to chronic complications in diabetes patients;[6] hence, the importance of lowering BG stably rather than quickly has been emphasized in recent years.

Modern medicine can control BG levels, but it has limited effects on improving patients' symptoms and controlling complications. TCM treatment is chosen according to TCM syndrome differentiation, and plays an important role in the treatment of T2DM and its complications in China.[7] Diabetes has a long history in TCM, and was first discussed in the book *Huang Di Nei Jing* under the name of Xiaoke.[8] Chinese doctors in ancient years thought that *Yin* deficiency and dry Heat were the pathogenesis of diabetes accompanied by symptoms of large intake of food and drink, polyuria, and emaciation. However, changes in lifestyle and environment are changing the symptoms of diabetes, especially T2DM and its TCM syndrome differentiation. Currently, internal Damp and Blood stasis play an important role in the development of T2DM.[9]

Different clinical manifestations can be found in different T2DM patients in clinical practice. For example, some individuals suffer from diabetes without discomfort, while others manifest with typical symptoms. Previous CGMS studies have demonstrated that glycemic profiles differ from person to person.[10,11] Thus, in this study we selected three types of common T2DM TCM syndromes, including intrinsic Damp syndrome, *Yin* deficiency and internal Heat syndrome, and *Qi* and *Yin* deficiency syndrome. Intrinsic Damp syndrome manifests as a heavy sensation of the body and limbs, abdominal distention, oppressed feelings in the chest, poor appetite, a sticky and greasy tongue with a white-thick coating, and a slippery pulse. *Yin* deficiency and internal Heat syndrome manifests as overeating and large appetite, thirst and excessive cold drinking, vexation, sensitivity to heat, insomnia, dry stool, yellow urine with constipation, a red tongue with yellow coating, and a fast and stringy pulse. *Qi* and *Yin* deficiency syndrome manifests as tiredness, spontaneous sweating, shortness of breath, thirst and excessive drinking, dysphoria with a hot sensation in the chest, palms and soles, palpitations and insomnia, red tongue with little or no coating, and a thready and weak pulse or a stringy and weak pulse. We explored the relationship between BG profile and TCM syndrome differentiation, expecting to provide evidence and instructions for selection of prescriptions in TCM clinical practice.

MATERIALS AND METHODS

Subjects

We recruited 109 in-patients from the Department of Endocrinology and the Department of TCM at the Sixth People's Hospital affiliated to Shanghai Jiao Tong University between 1 January 2012 and 30 June 2013. All patients gave informed consent, and the trial was approved by the Ethics Committee of the Sixth People's Hospital affiliated to Shanghai Jiao Tong University. The subjects were divided into three groups: group 1 included those with intrinsic Damp syndrome (n = 42), group 2 included those with *Yin* deficiency and internal Heat syndrome (n = 25), and group 3 included those with *Qi* and *Yin* deficiency syndrome (n = 42).

Standard of diagnosis

T2DM was diagnosed according to the 1999 World Health Organization (WHO) criteria.[12] TCM diabetes was diagnosed according to the standard in the 2002 Guidelines for Clinical Research into New Chinese Drugs.[13]

Inclusion criteria

T2DM patients aged 20-80 years were eligible for enrollment in this study if they were diagnosed with intrinsic Damp syndrome, *Yin* deficiency and internal Heat syndrome, or *Qi* and *Yin* deficiency syndrome according to TCM syndrome differentiation, and voluntarily agreed to take part in clinical observation. Additionally, only those who had not changed their treatment regimen in the previous 3 months were selected. All study subjects must not have changed their therapy until the CGMS was removed.

Exclusion criteria

(a) Patients aged ≥ 80 years or ≤ 20 years. (b) Acute complications including diabetic ketoacidosis and hyperglycemic hyperosmolar state in the previous month. (c) History of hepatic or renal impairment. (d) Other diseases which can influence glucose metabolism such as recent acute cerebral stoke, acute myocardial infarction, malnutrition, cancers and infections. (e) Patients who had changed their glucose-lowering regimen in the previous 3 months. (f) Patients who were unwilling to cooperate, such as those with mental disease. (g) Patients using drugs that influence glucose metabolism, such as hormones. (h) Patients diagnosed with other types of TCM syndromes.

Measurements and parameters

Study subjects were given a physical examination including measurement of height, weight, waist circumference, and hip circumference. Body mass index (BMI) was calculated as weight in kg divided by height in m^2. Blood pressure was measured in an air-conditioned, quiet room by using a mercury sphygmomanometer (OMRON Co., Ltd., Dalian, China); the average of three measurements taken at 2 min intervals was used for analysis.

The sensor of a retrospective CGMS was inserted, then removed after 72 h, generating a daily record of 288 continuous sensor values taken at 5 min intervals over 24 h. The CGMS was calibrated daily by entering a minimum of four capillary BG readings measured with a SureStep BG meter (LifeScan, Milpitas, CA, USA). A venous blood sample was drawn at 6am after a 10 h overnight fast to measure biochemical indicators, including hepatic biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and renal function biomarkers such as blood urea nitrogen (BUN), plasma creatinine (Cr), and uric acid (UA). Total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), 30 min postprandial plasma glucose (30PG), 120 min postprandial plasma glucose (120PG), HBA1C, and glycated albumin (GA) were also measured. Fasting C-peptide (FCp), 30 min postprandial C-peptide (30Cp), and 120 min postprandial C-peptide (120Cp) were monitored to evaluate β cell function. Ten individuals were selected randomly from each group to take an arginine test in order to accurately determine the β cell function of the pancreatic islets. The 24 h mean BG (MBG) level, total time in min in which subcutaneous glucose was over 10 mmol/L or less than 4 mmol/L, the maximum glucose level and the minimum glucose level were recorded to assess BG level. The standard deviation of BG values (SDBG), the mean amplitude of glycemic excursions (MAGE), mean of daily difference (MODD), and the large amplitude of glycemic excursions (LAGE) were calculated to estimate the state of glycemic variability.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences 17.0 (SPSS Inc., Chicago, IL, USA). Qualitative data are expressed as mean ± standard deviation ($\bar{x} \pm s$). The Kolmogorove-Smirnov normality test was done, and one-way analysis of variance (ANOVA) was employed if the data were normally distributed; the lowest significant difference or Student-Newman-Keuls multiple comparison in ANOVA was used to explore the difference between two groups. The rank sum test was used if the data were not normally distributed. Comparison of categorical variables was done using the χ^2 test; χ^2 was used when the minimum expected count $T \geq 5$, continuity correlation χ^2 was used when $1 \leq T < 5$, and Fisher's exact probability test was used when $T < 1$ or 0 appeared in the actual frequency. $P < 0.05$ was considered to denote statistically significant differences.

RESULTS

Baseline data

Characteristics of the patients in each group are shown in Table 1. Individuals in group 3 were much younger than those in group 2, and those in group 1 had the largest mean BMI and the highest mean systolic blood pressure compared with individuals in the other two groups (Table 1). Moreover, the mean TC in group 1 was significantly higher than that in groups 2 and 3 (all $P < 0.05$), and the mean blood UA was significantly higher in group 1 than in group 2 and 3 ($P < 0.01$, $P < 0.05$ respectively). In addition, there was a significant difference in mean ALT between patients in group 3 and those in the other two groups (all $P < 0.05$).

All patients being treated with insulin were using premixed insulin (Novolin 30R or Humulin 70/30) twice daily, before breakfast and before supper. Patients in the three groups were mainly treated with insulin and two kinds of oral hypoglycemic drugs (Table 2). Patients in group 2 were commonly using insulin combined with α-glucosidase inhibitors (α-GI) and sulfonylurea (SU), with fewer patients using metformin. More patients in group 1 were using statins to lower cholesterol compared with group 2 ($P < 0.01$).

Blood glucose level

Almost all indicators were normally distributed, except for time of BG < 4 mmol/L. FPG and 120PG were significantly higher in group 2 and significantly lower in group 3 among the three groups (all $P < 0.01$). 30PG and HBA1C were highest in group 2, although no significant differences in these two parameters were found between groups 1 and 3. GA in group 3 was much higher than in group 2, but there was no significant difference between GA in group 1 and the other two groups ($P > 0.05$). MBG, maximum BG, and time of BG > 10 mmol/L in group 2 were significantly higher

Table 1 Characteristics of patients with type 2 diabetes in each group ($\bar{x} \pm s$)

Characteristic	Group 1 (n = 42)	Group 2 (n = 25)	Group 3 (n = 42)
Male/Female (n)	18/24	12/13	27/15
Age (years)	57.15±8.32	60.36±8.97	54.95±11.90[a]
Height (cm)	163.5±7.83	164.36±8.67	165.98±9.15
Weight (kg)	68.78±10.19[a]	62.52±10.00[c]	65.81±10.39
BMI (kg/m^2)	25.73±3.35[b]	22.78±2.14[d]	24.01±3.33[c]
WC (cm)	92.98±10.38	88.35±7.13	90.25±10.32
HC (cm)	99.17±7.38	95.40±5.64	94.78±11.41[c]
SBP (mm Hg)	137.84±19.47[b]	127.04±13.87[d]	127.52±12.87[d]
DBP (mm Hg)	80.92±13.04	78.72±7.79	79.86±10.59
History of high BP (years)	10.40±9.42	8.50±9.20	16.00±13.11
Diabetes Duration (years)	10.84±6.82	11.21±7.26	10.66±7.48
TC (mmol/L)	4.50±1.32	4.56±1.00	4.36±0.72
TG (mmol/L)	2.36±1.75[a]	1.57±0.62[c]	1.63±1.06[c]
HDL (mmol/L)	0.99±0.21	0.95±0.23	1.04±0.30
LDL (mmol/L)	2.55±0.88	2.55±0.88	2.59±0.58
ALT (u/L)	19.13±10.14	18.68±7.59	26.69±18.04[ac]
AST (u/L)	19.18±5.80	17.28±5.65	21.90±8.78[a]
BUN (mmol/L)	4.85±1.90	5.42±1.97	4.95±1.94
Cr (μmmol/L)	64.36±20.13	75.80±39.94	69.78±24.89
UA (μmmol/L)	319.56±52.35[b]	272.50±55.49[d]	288.68±64.87[c]

Notes: group 1: intrinsic damp syndrome group; group 2: *Yin* deficiency and internal heat syndrome group; group 3: *Qi* deficiency and *Yin* deficiency syndrome group. As enrolled patients had a long duration of type 2 diabetes mellitus, all patients had been treated with insulin; no patient was being treated with oral hypoglycemic drugs alone. BMI: body mass index; WC: waist circumference; HC: hip circumference; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: plasma creatinine; UA: uric acid. [a]$P < 0.05$, and [b]$P < 0.01$, compared with group 2. [c]$P < 0.05$, and [d]$P < 0.01$, compared with group 1.

Table 2 Specific medication uses in each group (n)

Item	Medication use	Group 1 (n = 42)	Group 2 (n = 25)	Group 3 (n = 42)	Total
Hypoglycemic medication use	INS	0	0	2	2
	INS+α-GI	4	3	7	14
	INS+metformin	8	1	3	12
	INS+SU	4	3	5	12
	INS1	12[a]	2[c]	10[a]	24
	INS2	3[b]	11[d]	8[a]	22
	INS3	7	3	5	15
	INS4	4	2	2	8
	Total	42	25	42	109
Lipid lowering medication use	Statins	33[b]	11[d]	29	73
	Fibrates	2	0	0	2
	Total	35	11	29	75

Notes: group 1: intrinsic damp syndrome group; group 2: *Yin* deficiency and internal heat syndrome group; group 3: *Qi* deficiency and *Yin* deficiency syndrome group. As enrolled patients had a long duration of type 2 diabetes mellitus, all patients had been treated with insulin; no patients was being treated with oral hypoglycemic drugs alone. INS: insulin; α-GI: α-glucosidase inhibitors; SU: sulfonylurea; INS1: insulin and α-GI and metformin; INS2: insulin and α-GI and SU; INS3: insulin and metformin and SU; INS4: insulin and α-GI and metformin and SU. [a]$P < 0.01$, and [b]$P < 0.05$, compared with group 2. [c]$P < 0.01$, and [d]$P < 0.05$, compared with group 1.

than the other two groups, and significant differences were found between any two groups of the three (all $P < 0.01$). In group 2, the minimum BG was higher and time of BG < 4 mmol/L was less than the other two groups, although no significant difference was found between groups 1 and 3 (Table 3).

Glycemic variability

Data regarding indicators were normally distributed in group 2 and group 3, except for low BG index (LBGI). The SD, LAGE, MAGE, MODD, and M values were used to determine the state of BG fluctuations. The abovementioned parameters that reflect glycemic variability and the instability index (II), which is data standing the state of glucose instability, were all significantly lower in group 3 than the other two groups (Table 3, all $P < 0.01$). The LBGI in group 2 was significantly lower than in groups 1 and 3 ($P < 0.01$, $P < 0.05$ respectively), and the high BG index (HBGI) was highest in group 2. Glycemic risk assessment in diabetes equation (GRADE) was the indicator used to evaluate the risk of T2DM patients developing acute and chronic complications; the GRADE of group 2 > group 1 > group 3. Specific situations of glycemic variability in each group are shown in Table 4.

Table 3 Characteristics of blood glucose in the three groups ($\bar{x} \pm s$)

Characteristic	Group 1 (n = 42)	Group 2 (n = 25)	Group 3 (n = 42)
FPG (mmol/L)	8.2±2.8[a]	9.8±2.7[c]	7.0±1.7[ad]
30PG (mmol/L)	10.8±3.1[b]	12.9±3.7[d]	9.5±2.5[a]
120PG (mmol/L)	13.4±3.7[a]	16.2±3.5[c]	10.6±3.6[ac]
HBA1C (%)	8.7±1.8[b]	9.7±1.7[d]	8.1±1.9[a]
GA (%)	20.9±5.8	23.4±5.2	18.5±5.4[a]
MBG (mmol/L)	9.8±2.1[a]	11.4±2.0[c]	8.0±1.4[ac]
Maximum of BG (mmol/L)	16.4±3.1[a]	18.2±2.5[c]	13.1±2.6[ac]
Minimum of BG (mmol/L)	4.6±1.7[a]	6.5±2.2[c]	4.8±1.3[a]
Time of BG > 10 mmol/l (min)	626.7±320.8[a]	860.8±312.2[c]	243.6±223.2[ac]
Time of BG < 4 mmol/L(min)	36.3±82.7[b]	4.2±23.9[d]	36.1±89.3[b]

Notes: group 1: intrinsic Damp syndrome group; group 2: *Yin* deficiency and internal Heat syndrome group; group 3: *Qi* deficiency and *Yin* deficiency syndrome group. As the enrolled patients had a long duration of type 2 diabetes mellitus, all patients were being treated with insulin; no patient was being treated with oral hypoglycemic drugs alone. FPG: fasting plasma glucose; 30PG: 30 min postprandial plasma glucose; 120PG: 120 min postprandial plasma glucose; HBA1C: glycolated hemoglobin; GA: glycated albumin; BG: blood glucose; MBG: 24 h mean blood glucose. Indicators in Table 3 were normally distributed, except for time of BG < 4 mmol/L, so the rank sum test was used to compare time of BG < 4 mmol/L between two groups. [a]$P < 0.01$, and [b]$P < 0.05$, compared with group 2; [c]$P < 0.01$, and [d]$P < 0.05$, compared with group 1.

Table 4 Characteristics of glycemic variability in the three groups ($\bar{x} \pm s$)

Characteristic	Group 1 (n = 42)	Group 2 (n = 25)	Group 3 (n = 42)
SD	2.8±1.0	3.0±0.9	1.9±0.7[ac]
LAGE (mmol/L)	11.7±3.4	11.7±2.9	8.3±2.7[ac]
MAGE (mmol/L)	6.8±3.1	7.2±2.5	5.2±2.4[ac]
MODD (mmol/L)	2.8±1.0	3.0±1.0	2.0±0. 8[ac]
II [(mmol/L)^2/L per day]	5.3±3.7	4.5±1.6	3.2±2.2[ac]
LBGI	3.1±3.4[a]	0.7±1.3[c]	1.9±3.1[b]
HBGI	11.1±6.1[b]	15.0±6.5[d]	4.9±3.2[ac]
GRADE	9.6±5.3[a]	13.1±4.7[c]	5.1±2.9[ac]
M value	19.9±16.1[b]	30.1±17.6[d]	7.1±6.1[ac]

Notes: group 1: intrinsic damp syndrome group; group 2: *Yin* deficiency and internal heat syndrome group; group 3: *Qi* deficiency and *Yin* deficiency syndrome group. As enrolled patients had a long duration of type 2 diabetes mellitus, all patients had been treated with insulin; no patient was being treated with oral hypoglycemic drugs alone. SDBG: standard deviation of blood glucose values; MAGE: mean amplitude of glycemic excursions; MODD: mean of daily difference; LAGE: large amplitude of glycemic excursions; II: instability index; LBGI: low blood glucose index; HBGI: high blood glucose index; GRADE: glycemic risk assessment in diabetes equation. LBGI data were not normally distributed in group 2 and group 3, so the rank sum test was used to compare the indicator among groups. [a]$P < 0.01$, and [b]$P < 0.05$, compared with group 2; [c]$P < 0.01$ and [d]$P < 0.05$, compared with group 1.

β *cell function*

The β cell function data distribution was normal (Table 5). The change in the C-peptide value (△Cp) was used to make a simple evaluation about β cell function. The increase in 30 Cp was less than that in 120Cp (Table 4). No significant difference was found in FCp or 30 Cp among the three groups; however, the FCp in group 1 seemed higher than the other two groups, and the level of 120 Cp in group 3 was the highest among the three groups (all $P < 0.05$). The increase in C-peptide after 120 min (△Cp120) in group 3 was significantly higher than in groups 1 and 2 (all $P < 0.05$). In order to obtain acute results regarding β cell function, we selected 10 patients randomly in each group using a lottery method to take an arginine trial; the results of this showed that patients in group 1 had the worst β cell function, and the best β function was in group 3. Beta cell function in group 3 > group 2 > group 1 (Figure 1, Table 5).

DISCUSSION

Recognition of diabetes mellitus (DM) in TCM originated from the Su Wen, and was termed xiaoke;[14] the disease manifested as large intake of food and drink, polyuria, and emaciation. TCM explores the occurrence of DM in terms of cause, onset, pathogenesis, disease characteristics, and relationship between evil *Qi* and vital energy.[15] In TCM, DM is an individualized disease caused by *Yin* deficiency and dry Heat, with *Yin* deficiency as the basis of the disease. However, in recent years, an increasing number of TCM doctors have considered that DM was a part of Xiaoke that cannot summarize the whole features of DM. In other words, one part of DM can be treated as xiaoke, but the other part cannot. For example, patients who have a rise in BG according to the diagnostic criteria for DM in modern medicine but do not have diabetic symptoms are beyond the scope of xiaoke. Thus, modern TCM doctors have different viewpoints in recognizing DM from TCM doctors in ancient years.

Given that syndrome differentiation is the essence of TCM, DM patients are always classified into kinds of syndromes to allow individual treatment in TCM clinical practice. While it was previously thought that *Yin* deficiency and internal Heat was the most common syndrome of DM, doctors in clinical practice have found that intrinsic Damp syndrome is playing a more important role in development of the disease in recent years.[9] Moreover, many studies have reported that intrinsic Damp syndrome is now one of the most common syndromes in DM, accounting for 14.1% of all TCM syndromes in DM patients.[16] The importance of invigorating the Spleen has been emphasized in clinical TCM,[17] which further indicates that internal wetness plays an important role in DM as Damp always results from deficiency of the Spleen.

In this study, three common TCM syndromes in DM patients including *Qi* and *Yin* deficiency syndrome, *Yin* deficiency and internal Heat syndrome, and intrinsic Damp syndrome were selected to explore the glycemic features of different syndromes. CGMS measurements showed that the BG profile of T2DM patients with *Qi* and *Yin* deficiency syndrome was more stable and had the lowest level of glycemic variability, while patients in the other two groups had fluctuating BG profiles. In addition, the MBG of subjects with *Yin* deficiency and internal Heat syndrome was the highest among the three groups.

C-peptide is a product of proinsulin decomposition; hence, the △Cp was used to assess the β cell function of T2DM patients as all enrolled patients were using insulin to control BG, which would influence the total level of blood insulin. β cell function in those with *Qi* and *Yin* deficiency syndrome was better than that in the other two groups; however, there seems to be a slight deviation in results when we use the method of △Cp or the arginine test to assess β cell function in those with *Yin* deficiency and internal Heat syndrome. There is a possibility that this results from toxicity of hyperglycemia, which might suppress the response of the islet cells to sugar (carbo-

Table 5 Beta cell function in each group (mU/L, $\bar{x} \pm s$)

Beta cell function	Group 1 (n = 42)	Group 2 (n = 25)	Group 3 (n = 42)
FCp	2.1±1.3	1.9±1.1	2.0±0.8
30Cp	2.7±2.1	2.5±1.4	3.4±1.9
120Cp	4.3±3.6	3.7±2.3	6.0±3.9[ab]
△Cp30	0.7±1.1	0.6±1.0	1.2±1.2[b]
△Cp120	2.3±2.7	2.0±1.8	3.7±3.2[ab]
Cp Index (n = 10)	1.0±0.6	1.4±0.8	1.9±0.9[a]
INS Index (n = 10)	14.2±7.7	19.8±16.2	30.9±20.4[a]

Notes: group 1: intrinsic damp syndrome group, group 2: *Yin* deficiency and internal heat syndrome group, group 3: *Qi* deficiency and *Yin* deficiency syndrome group. As the enrolled patients had a long duration of type 2 diabetes mellitus, all patients had been treated with insulin; no patients were being treated with oral hypoglycemic drugs alone. Cp: C-peptide; FCp: fasting C-peptide; 30Cp: 30 min postprandial C-peptide; 120Cp: 120 min postprandial C-peptide; △Cp30: change in C-peptide after 30 min; △Cp120: change in C-peptide after 120 min; INS: insulin. [a]$P < 0.05$, compared with group 1. [b]$P < 0.05$, compared with group 2.

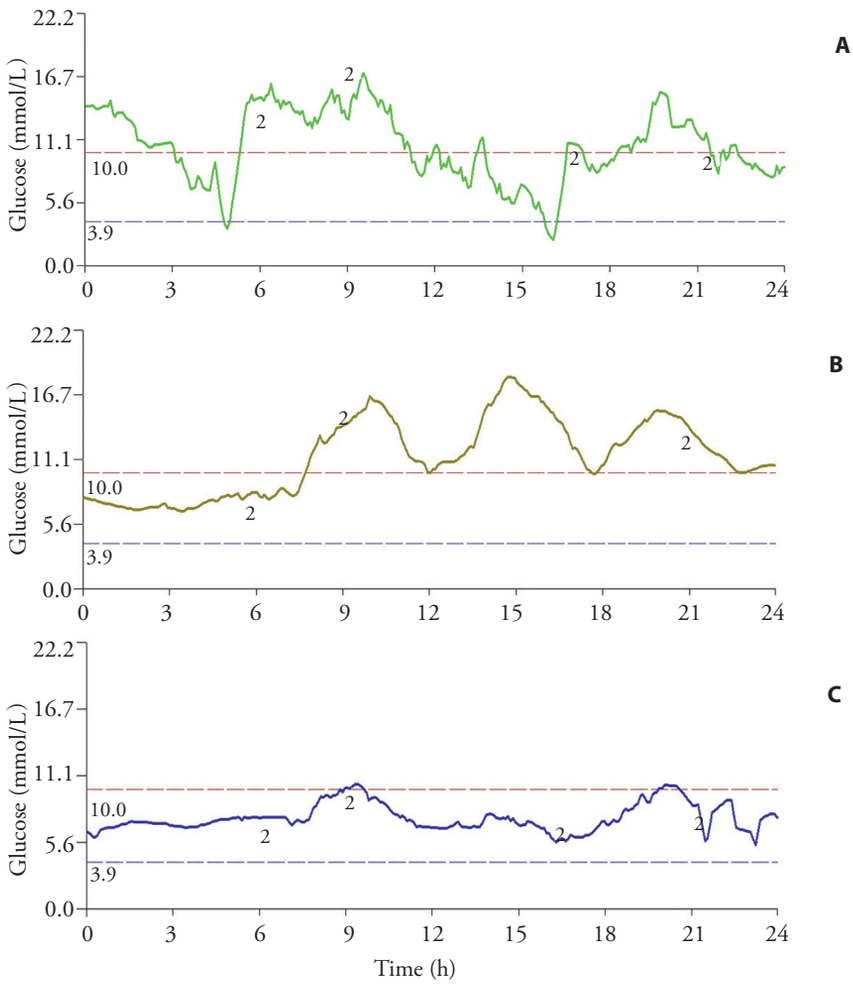

Figure 1 Blood glucose profile of type 2 diabetes mellitus patients with three different Traditional Chinese Medicine syndromes
A: blood glucose profile of a patient with intrinsic Damp syndrome. B: blood glucose profile of a patient with *Yin* deficiency and internal Heat syndrome. C: blood glucose profile of a patient with *Qi* deficiency and *Yin* deficiency syndrome. The red horizontal dotted line shows the hyperglycemia level (10.0 mmol/L), and the blue horizontal dotted line shows the hypoglycemic level (3.9 mmol/L). The "2" indicate the times when the CGMS was calibrated by entering capillary blood glucose readings measured using a SureStep blood glucose meter.

hydrate) but not to amino acids, including arginine.[18] In addition, Chinese diets are based mainly on carbohydrates.

As well as higher glycemic variability, there was a higher mean BMI, TG and systolic blood pressure found in those with intrinsic Damp syndrome. So BG, blood lipid, and blood viscosity in Western Medicine might be referred to as Damp turbidity in TCM.[19] There was no significant difference in TC, HDL-C and LDL-C among groups; the reason for this may be that many patients take statin drugs to control cholesterol levels as more attention has been paid to this indicator since the harms of cholesterol (especially LDL-C) on human health are extensively known. In contrast, TG, which has little relationship with DM complications, is always neglected.

There was no difference in HBA1C and GA between those with intrinsic Damp syndrome and those with *Qi* and *Yin* deficiency syndrome, although the MBG in those with intrinsic Damp syndrome was higher than that in those with *Qi* and *Yin* deficiency syndrome. The phenomenon referred above indicated that the MBG might have some relationship with BMI, which is associated with hepatic metabolism and chronic inflammation.[20] This was confirmed in our study by measuring the plasma ALT, a data reflecting hepatic metabolism; the ALT in those with intrinsic Damp syndrome was much lower than that in those with *Qi* and *Yin* deficiency syndrome. Furthermore, we also found that fewer patients with *Yin* deficiency and internal Heat syndrome were treated with metformin compared with those with intrinsic Damp syndrome, which can be explained by the lower BMI of patients with *Yin* deficiency and internal Heat syndrome. Since metformin can take a more important part in losing weight,[21] it will not be firstly considered if patients had a lower BMI.

Our results regarding BG fluctuations and β cell function indicate that different TCM syndromes might reflect the onset of T2DM, which is contrary to the conclusions of Duan *et al.*[22] *Qi* and *Yin* deficiency syndrome is the foundation of T2DM, as reported in the ancient literature. For example, the *Ling Shu 'Wu Bian'* states that individuals with deficiency in the five

Zang organs are susceptible to xiaodan.[23] The *Ling Shu 'Xie Qi Zang Fu Xing'* also states that subjects with weak pulse of the five *Zang* organs were all xiaodan, declaring that people with deficiency of the five *Zang* organs and both *Qi* and Blood shortage were susceptible to the disease.[24] Above all, deficiency is the base of DM, which is also a saying from the *Huang Di Nei Jing*[8] consistent with our conclusions. Yet the disease can develop from the *Qi* and *Yin* deficiency stage into the intrinsic Damp stage or *Yin* deficiency and internal Heat stage, developing an orientation that is closely associated with patients' physical constitution and their eating habits. It is explained in the *Su Wen 'Qi Bing Lun'* that most obese people must have eaten too much sweet and fatty food. Internal Heat generated by fatty food, and abdominal distention induced by sweet food make ascending *Qi* form DM[8]; this emphasizes the importance of diet in the occurrence of DM.

However, not every patient will begin with deficiency and go through all stages of the disease, as DM is a disease closely related to the individuals' constitution. Therefore, in clinical TCM practice, individualized classification of patients should be based on the patient's own BG profile and clinical symptoms. Heat-clearing herbs should be prescribed if the MBG is high, but when the BG fluctuation is patent, herbs with the effect of nourishing *Yin* and clearing Heat or invigorating the Spleen and eliminating Dampness can be chosen. Additionally, methods of supplementing *Qi*, nourishing *Yin*, and activating Blood circulation can be used to delay the incidence of complications when the BG profile is relatively stable.

In this study we explored the characteristics of glycemic variability of T2DM in patients with *Qi* and *Yin* deficiency syndrome, *Yin* deficiency and internal Heat syndrome, and intrinsic Damp syndrome. This information can lay the foundation for diagnosis and treatment of T2DM in TCM, and provide data for further research. However, there are several limitations of this study. We only selected three common syndromes with a small sample size, we did not record the use of antihypertensive drugs, and we only analyzed fluctuations of BG but without exploring other laws about BG level such as characteristics of BG in the daytime and at night. Moreover, we only chose T2DM patients already in treatment, and did not include newly diagnosed patients or those with impaired glucose tolerance (IGT). In addition, the clamp test was not done to accurately assess the pancreatic islet function of patients. Further detailed prospective studies into the characteristics of BG profiles in newly diagnosed T2DM and IGT patients with a large sample size are needed to provide information on syndrome differentiation and selection of prescriptions in clinical TCM practice.

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